UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/541,094 | 03/31/2000 | Peter H. St. George-Hyslop | 1034/1F812-US2 | 4017 |

7590 01/30/2003

Darby & Darby P C
805 Third Avenue
New York, NY 10022

| EXAMINER |
|---|
| WOITACH, JOSEPH T |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 19 |

DATE MAILED: 01/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

| Office Action Summary | Application No. 09/541,094 | Applicant(s) St. George-Hyslop et al. |
|---|---|---|
| | Examiner Joseph Woitach | Art Unit 1632 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) [X] Responsive to communication(s) filed on *Nov 12, 2002*

2a) [ ] This action is **FINAL**. 2b) [X] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) [X] Claim(s) *42, 47, 49, 50, 52-54, 56-61, 63, and 65* is/are pending in the application.

4a) Of the above, claim(s) *42* is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *47, 49, 50, 52-54, and 56-61* is/are rejected.

7) [X] Claim(s) *63 and 65* is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) [X] The specification is objected to by the Examiner.

10) [X] The drawing(s) filed on *Mar 31, 2000* is/are a) [X] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [X] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) [X] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948).
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) [ ] Interview Summary (PTO-413) Paper No(s). _____
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other:

***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 12, 2002, paper number 18, has been entered.

**DETAILED ACTION**

This application claims benefit to provisional applications 60/127,452, filed April 1, 1999, and 60/173,826, filed December 30, 1999.

As indicated in Applicants' request for continued examination the After final amendment filed September 12, 2002, paper number 15, has been entered. Claims 1-6, 18-28, 30, 46, 48, 51, 55, 62 and 64 have canceled. Claims 47, 49, 50, 52-54, 56, 59, 60, 63 and 65 have been amended. Claims 42, 47, 49-50, 52-54, 56-61, 63 and 65 are pending. Claim 42 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10. Claims 47, 49-50, 52-54, 56-61, 63 and 65 are

currently under examination as they are drawn to the elected invention of human PAMP nucleic acid sequences.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

***Oath/Declaration***

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It was not executed in accordance with either 37 CFR 1.66 or 1.68. Specifically, the specification was filed with a preliminary amendment and an unexecuted declaration. A signed declaration was filed November 27, 2000, paper number 3, however the declaration did not specifically refer to the preliminary amendment. A substitute declaration or oath to correct the deficiencies clearly indicating the application serial number and indicating 'as amended in the preliminary amendment filed March 31, 2000' is required. See MPEP 604.08.

***Priority***

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 47, 49-50, 52-54, 56-61, 63 and 65 of this application. It is well settled that "[I]t is not enough for purposes of written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modification that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.* (Fed. Cir. March 1997) 41 USQP2d 1961 at 1966. In the instant case as compared to SEQ ID NO: 2 (disclosed in the provisional application) SEQ ID NO: 14 comprises 23 additional amino acid residues which would have not been obvious in light of SEQ ID NO: 2 or the general description provided by the specification. Because the SEQ ID NOs specifically claimed and encompassed by the present claims were not fully supported in the provisional applications, the priority of given to the instant claims is the filing date of the instant application, March 31, 2000.

***Specification***

The disclosure is objected to because of the following informalities:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See for example page 9, lines 6 and 26 and page 38, line 26.

Applicant is required to delete all embedded hyperlink and/or other form of browser-executable code from the specification. See MPEP § 608.01.

Appropriate correction is required.

Additionally, the specification makes reference to specific figures which are not present in the present disclosure. The specification was filed with one figure, Figure 1A and 1B, (see figures submitted and as evidenced in the amendment filed January 31, 2001, paper number 8), however the specification indicates that results are illustrated in figures 6 and 8 (see page 40, lines 20-25). It is unclear if this is an error in the specification or if Applicants have failed to provide the figures indicated in the specification.

Clarification and appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47, 49-50, 52-54, 56-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 52 and 54 are in the recitation of 'a function-conservative variant' because this term is not specifically defined in the specification and the metes and bounds of the claims can

not be determined because what functions are to be conserved is not clearly set forth. It is not clear if the claim encompasses any function that a polypeptide having 60% homology to SEQ ID NO: 14 maintains, maintaining all the inherent properties of the wild type PAMP, encompasses simply the activity of binding presenilin, or that it encompasses some variant of any of these functions. Claims 63 and 65 are not included in the basis of the rejection because they encompass only SEQ ID NO 14.

Claim 58 is unclear because it is dependent on canceled claim 55. It is unclear if claim 58 is meant to embody the limitations of claim 55 or is dependent on another pending claim. The metes and bounds of the claim are indefinite because the specific limitations of the claims encompassed by the claim are not clearly set forth. Rewriting the claim as an independent claim or amending the dependency of the claim to a pending claim would obviate the basis of the rejection.

Claims 47, 49, 53, 56 and 58 are unclear and ambiguous in the recitation of 'PAMP (SEQ ID NO: X)' because the specification does not specifically define PAMP as a SEQ ID NO and provides a description of structural features of PAMP relative to the protein encoded by SEQ ID NO: 14 including (pages 8-10). Further, the specification states that the 'term "PAMP" also refers to active fragments of the protein (page 10, lines 11-12), naturally occurring variants (page 10, lines 19-20), and mutant forms (page 10, line 23). The claim is unclear because language clearly indicating whether the specific SEQ ID NO is being claimed or that the SEQ ID NO serves as an example of the term PAMP is not clearly set forth. The metes and bounds of the

claim are unclear because it is not clear if the claim encompasses only the specific SEQ ID NO or if it encompasses any PAMP as exemplified by the SEQ ID NO. Amending the claim to indicate the limitation of 'PAMP as set forth in SEQ ID NO: X' or specifically claiming the SEQ ID NO would obviate the basis of the rejection. Dependent claims 50, 59, 60, 61 are included in the basis of the rejection because they fail to further clarify the basis of the rejection and only set forth that the sequence is comprised in a vector, comprise specific alterations of the amino acid sequence or methods of use of said vector.

identity, (page 17, lines 8-24)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47, 49-50, 52-54, 56-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 52 recites and encompasses 'function-conservative variants of human PAMP'. As noted above in the rejection made under 35 USC 112, second paragraph, claims 47, 49 and 53 can also be interpreted to encompass this embodiment as well as active fragments of the protein,

naturally occurring variants, and mutant forms of PAMP. Dependent claims 50, 54, 56-61 are included in the basis of the rejection because they are drawn to products and methods which require mutant variant PAMP sequences. Claims 63 and 65 are not included in the rejection because they are limited to a single specific human PAMP sequence. The specification discloses a single human polynucleotide sequence for PAMP (SEQ ID NO: 14), and defines the polypeptide produced from the open reading frame as SEQ ID NO: 13. The specification does not disclose any other species 'wild type' human polynucleotide sequences which would be considered variants or any active fragments and mutant forms of PAMP. Applicants note that the specification describes a function-conservative variant which provides the literal support for the claim, and argue that by providing specific sequence homology and functional language to the protein produced by the polynucleotide the specification has demonstrated that the inventors were in possession of the claimed invention and that the claims comply with the written description requirement. See Applicants' amendment pages 6-9. Applicants arguments have been fully considered but not found persuasive. Initially, the functional language recited and relied upon in the claim 'capable of interacting with a presenilin' relates to the PAMP protein, not the polynucleotide instantly claimed. Therefore, this limitation does not describe the polynucleotide which is claimed, rather it describes one property of the PAMP protein encoded by SEQ ID NO: 13. The only functional limitation in the claim related to the polynucleotide is that it encodes a 'function-conservative variant' which is described in the specification as 'a given amino acid residue in a protein or enzyme [which] has been changed without altering the

overall conformation and function of the polypeptide' and indicates that the changes can comprise differences of 60% to 99% as long as the resulting protein has 'the same or substantially the same properties or functions as the native or parent protein' (page 17). This portion of the specification only provides a general outline which can be applied to any protein, and is silent with respect to any specific changes to the PAMP protein. Again, the functional limitations recited in the claim are directed to the protein produced and not the polynucleotide which is claimed. While one may be able to produce variant PAMP proteins from an altered SEQ ID NO 13 polynucleotide sequence, such is not at issue. What is at issue is whether the specification as filed, provides adequate written description of such polynucleotides or variant PAMP polypeptides encoded by a polynucleotide.

The courts have stated that: 'The written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics...i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of characteristics. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F 3d at 1324, 63 USPQ2d at 1613 (Fd Cir 2002).

The court has also addressed the issue of what constitutes adequate written description of a claim to a broad genus of sequences Applicants attention is drawn to the decision of *The Regents of the University of California v. Eli Lilly and Company* (CAFC, July 1997) wherein it was stated: 'In claims involving chemical materials, generic formulas usually indicate with

specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate written description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See *Fiers,* 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen*). It is only a definition of a useful result rather than a definition of what it achieves as a result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. *See In re Wilder*, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, indicating generally that a variant protein maintains a property of the parent protein

generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

As indicated above, Examiner would concede that the artisan can make variant PAMP proteins and test the variants for a specific properties, however this is not sufficient to meet the written description requirement. The courts have stated that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). Therefore, while one may make and test all the possible variant sequences encompassed by the claim, the specification fails to provide the necessary description to which of all these possible variants would retain any function of the parent molecule.

In analyzing whether the written description requirement is met by disclosure of a sufficient number of species, it is first determined whether the whether a representative number of species have been described by their complete structure. In the instant case the claims encompass an enormous number of variant polynucleotide sequences which is defined by a property of a protein produced from said polynucleotide, however only one human PAMP sequence, SEQ ID NO: 14 is disclosed. With the limited information disclosed in the specification, the artisan does not have the necessary guidance to whether any other human sequence besides SEQ ID NO: 14 exist in nature or that any variant would have a functional conservative property of PAMP. The specific mutants set forth in claims 56, 57 and 58 are

characterized in the specification, however the specification teaches that the deletion mutants do not bind presenilin, and expression of the other mutants in cells result phenotypic characteristics different than that of wild type PAMP clearly indicating that the mutants do not have the same properties as wild type PAMP (mutants characterized on pages 43-45). Therefore, these examples would not be representative a function-conservative variant. The single example of one human PAMP polynucleotide sequence does not provide adequate disclosure for the infinite number of variant PAMP sequences encompassed by the claims.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. In the instant case, the recitation of function-conservative variant and embodiments of active fragments of the protein, naturally occurring variants, and mutant forms of PAMP, does not provide adequate description of the polynucleotides claimed. Thus, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited and encompassed by the claims at the time the application was filed. Thus, it is concluded that the written description requirement under 35 U.S.C. 112, first paragraph, is not satisfied for the claimed genera.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 47, 49-50, 52-54, 56-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using SEQ ID NO: 14, does not reasonably provide enablement for making and using any other functional variant of SEQ ID NO: 14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

As noted above in the rejection made under 35 USC 112, second paragraph, claims 47, 49 and 53 can also be interpreted to encompass this embodiment as well as active fragments of the protein, naturally occurring variants, and mutant forms of PAMP. Claim 52 recites and encompasses 'function-conservative variants of human PAMP'. The specification provides one human PAMP polynucleotide sequence as set forth in SEQ ID NO: 14, and is silent with respect to any other specific sequence of a variant of SEQ ID NO: 14 that encodes a function-conservative variant polypeptide or any functional fragment thereof. With respect to protein variants encoded by the instantly claimed polynucleotide, the specification provides general guidance for making alterations which could apply to making alterations to any protein, but is silent with respect to specific guidance on alterations which could be made in the human PAMP sequence which would result in a protein with a conserved function. The only specific function ascribed to the PAMP protein is the ability to bind preselin. With respect to the specific mutants set forth in claims 56, 57 and 58, the specification teaches that the deletion mutants do not bind preselin, and expression of the other mutants in cells result phenotypic characteristics different than that of wild type PAMP clearly indicating that the mutants do not have the same properties as wild type PAMP (mutants characterized on pages 43-45). Given only the general guidance for making alterations and the only specific examples are non-functional variants, the skilled artisan would not be able to predict the structure of a variant that is biologically active because the specification has not provided any information as to the structural elements required for a function-conservative variant PAMP. The specification does not provide any information on

what amino acid residues are necessary and sufficient for any biological activity. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in a variant polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there are no other examples of a human variant known that have structural homology with SEQ ID NO: 14, it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation.

Furthermore, it is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz *et al.* (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976) discloses that even for peptide hormones, which are much smaller than the instant lipase protein, one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "case to case painstaking experimental study" to determine active variants (see page 7). Consequently, excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence

derivatives encoding a biologically active lipase with an amino acid sequence differing from SEQ ID NO: 14 since the amino acid sequence of such polypeptides could not be predicted.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative embodiments. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which can be tolerated in a protein's amino acid sequence and still retain similar biological activity requires a (1) knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which re conserved (*i.e.*, expectantly intolerant to modification), and (2) detailed knowledge of the ways in which the protein's structure relates to its function. However, as discussed above, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determination to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the real of routine experimentation.

One of the main considerations to be made in determining whether undue experimentation is required is the amount of experimentation required. See *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). Even if substitutions with the natural 20 amino acids encoded by DNA were the only modifications, instant claims would still broadly encompass a multitude of species; calculated as 20N * (length)!/N/(length-N)! wherein "20" is the number of natural amino

acids encoded by DNA, "N" is the number of positions where substitutions can occur, "!" is the factorial symbol, "/" is the division symbol and "length" is the total number of amino acids in the protein or peptide. In putting these numbers in perspective, it is noted that the earth is estimated to have existed for $10^{17}$ seconds (see Creighton, T.E. 1983. Proteins: Structure and Molecular Principles, W. H. Freeman and Company, NY. 93-94, page 94, paragraph 1). A polypeptide chain of 100 amino acids could exist in $10^{130}$ combinations and "just one molecule of each of these different proteins would fill the entire [known] universe $10^{27}$ times over, even if packed together in the most efficient manner" (see paragraph 1, page 94 Creighton).

While recombinant and mutagenic techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar biological activity are limited in any protein. The result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modifications in such proteins.

The specification does not support the broad scope of the claims which encompass all modifications and fragments because the specification does not disclose the following:

a) The amino acid sequence for the claimed variant protein;

b) The general tolerance to modification and extent of such tolerance;

c) The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;

d) What fragments, if any, can be made which retain the biological activity of the intact protein; and

f) The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, the specification has not provided sufficient guidance to enable one of skill in the art to make and use the claimed protein in a manner reasonably correlated with the scope of the claims, broadly including any number of additions, deletions, or substitutions and fragments of any size. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court: " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.'). Further, "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148

USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

In the instant case, this specification provides only a starting point. Given the art recognized unpredictability conserving function when altering amino acid sequences, the lack of specific guidance for alterations in PAMP which would result in a functional variant or fragment,

and the enormous number of possible variants encompassed by the claims which the artisan must test, it would have required undue experimentation to make and/or use the invention as claimed.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 47, 49, 50, 52, 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Genbank Accession Number D87442.

As discussed above in the rejection made under 35 U.S.C. 112, second paragraph, claims 47 and 49 can be interpreted to encompass polynucleotide sequences of PAMP as exemplified by SEQ ID NOs 14 and 13. The specification teaches the term PAMP includes active fragments of the protein (page 10, lines 11-12), naturally occurring variants (page 10, lines 19-20), and mutant forms (page 10, line 23). D87442 is a nucleic acid sequence which shares 99.9% identity with SEQ ID NO 13. Applicants argue that the genbank listing does not make reference about a protein. See Applicants' amendment, bottom of page 11. Applicants arguments are not persuasive because the title associated with the listing indicates that the disclosed cDNA sequence encodes one of eighty newly identified genes, and listed in the features of the sequence

the first codon is specifically indicated and identified with protein ID number for the encoded polypeptide. Because of the 99.9% identity, in particular over the domain which is proposed to interact with presenilin, the D87442 sequence would encode a function-conservative variant within the breadth encompassed by the claims. Additionally, the sequence was obtained from a cDNA library which was contained in the pBluescript II SK plasmid vector which has promoters as expression control sequences which is grown in *E. coli*, therefore D87442 discloses the sequence in a vector with control sequences. Claim 54 is not included in the basis of the rejection because while pBluescript and the *E. coli* host may be able to express the PAMP protein encoded by the sequence disclosed, it appears that the coding sequence was not in frame and thus not operatively linked to the promoter sequences in pBluescript.

***Conclusion***

No claim is allowed. Claims 63 and 65 are objected to for being dependent on rejected claims but would be found allowable if rewritten as independent claims encompassing the embodiments of the independent claim and any intervening claims. Claims 54, 56-61 are free of the art of record, however they are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

Joe Woitach

AU 1632